REMARKS

Reconsideration of this application is respectfully requested.

Prior to entering the amendments above, the status of the claims is as follows. Claims 569-595, 597-643, 645-646, 648-651, 654-679, 681-682, 684-687, 690-714, 716-717, 719-747, 749-797, 800-803, 806-831, 833-834, 836-839, 842-866, 868-869, 871-899, 901-947, 949-950, 952-955, 958-983, 985-986, 988-991, 994-1018, 1020-1021, 1023-1051, 1053-1099, 1101-1102, 1104-1107, 1110-1135, 1137-1138, 1140-1143, 1146-1170, 1172-1173, 11751250, 1252-1253, 1255-1258, 1261-1294, 1296-1407, 1409-1568, 1570-1612 and 1614-1768 were previously pending in this application.

Of those previously pending claims, the following claims have been allowed: claims 569-595, 597-599, 601-603, 625-633, 671-679, 684-687, 690-708, 719-722, 726-747, 753-755, 777-785, 823-831, 833-834, 836-839, 842-860, 871-899, 905-907, 929-937, 975-983, 985-986, 988-991, 994-1012, 1023-1026, 1030-1051, 1057-1058, 1082-1089, 1127-1135, 1137-1138, 1140-1143, 1146-1164, 1175-1176, 1247, 1700-1703, 1719-1722, 1729, 1742 and 1766.

I. Summary of Claim Amendments

Commensurate with their disclosure, Applicants have added new sequencing claims 1769-1775 above, each of which is limited to fluorescent or chemiluminescent indicators for detecting labeled nucleic acid fragments. New claim 1769 is independent and is directed to a process for determining the sequence of a nucleic acid of interest. Three steps are recited in claim 1769. The first step calls for "generating detectable non-radioactively labeled nucleic acid fragments complementary to said nucleic acid of interest or a portion thereof,

wherein said fragments have been labeled by incorporation of one or more detectable non-radioactive modified or labeled nucleoside triphosphates or analogs thereof, said nucleoside triphosphates or analogs comprising fluorescent or chemiluminescent indicators." The second step recites "subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments," followed by the third step of "detecting each of said separated or resolved fragments by means of the fluorescent or chemiluminescent indicators, to determine the sequence of said nucleic acid of interest." Thus, new sequencing claim 1769 is limited to the use of fluorescent or chemiluminescent indicators.

The new claims added above that ultimately depend from claim 1769 are directed to various embodiments:

the use of a sugar moiety or sugar analog in the generating step (claim 1770);

the sugar or sugar analog comprising a furanose selected from . . . ribose, deoxyribose, dideoxyribose and analogs thereof (claim 1771);

the use of a phosphate moiety or a phosphate analog in the generating step (claim 1772);

the use of a base moiety or a base analog in the generating step (claim 1773);

the base moiety or base analog comprising a purine, a purine analog, a pyrimidine, or a pyrimidine analog (claim 1774); and

the fluorescent or chemiluminescent indicators being attached to the base moiety or base analog (claim 1775).

Support for the subject matter of new claims 1769-1775 is found in the specification. See, for example, the specification, page 84, second paragraph. See also, page 96, last paragraph, continuing through page 97, first paragraph.

Entry of the above new claims is respectfully requested.

II. The Rejection Under 35 U.S.C. §112, First Paragraph (Enablement)

In the March 12, 2002 Office Action (pages 3-5), several claims were rejected under 35 U.S.C. §112, first paragraph,[1] because the specification, while being enabling for being limited to furanose moieties as the SM structure in the instant claims, "does not reasonably provide enablement for the generic limitation given as 'sugar'." The text of the Examiner's remarks is found on pages 3-5 in the March 12, 2002 Office Action.

In their September 12, 2002 Amendment (pages 15-16), Applicants responded as follows:

> This matter was discussed at some length during the interview held on September 5, 2002. Applicants would like to reiterate that the structure of the sugar moiety in nucleic acid polymers is not altogether critical for hybridization purposes. In the case, for example, where the sugar moiety resides at the terminus of the polymer or even within the nucleic acid polymer, hybridization is still permitted and will occur. In the present specification, Applicants disclose three sugar moieties in the form of ribose, deoxyribose and dideoxyribose, each of which can be the terminal sugar moiety in the polynucleotide chain. The former two, ribose and deoxyribose, can reside anywhere in the polynucleotide chain. Dideoxyribose is a chain terminator and will be present at the terminus. In his classic textbook, DNA Replication [Second Edition, W. H. Freeman and Company, New York, 1992], Dr. Arthur Kornberg reviews a number of sugar analogs in Chapter 14 ("Inhibitors of Replication"). Sugar analogs which are chain terminators are listed at the top of Table 14-3 ("Nucleotide analogs incorporated into DNA or RNA") on page 447. As explained by Dr. Kornberg on page 446 under "14-3 Nucleotide Analogs Incorporated into DNA or RNA:"
>
> > Certain analogs of the NTPs, modified in the sugar or base, are accepted by polymerases ***for pairing with the DNA template*** and

[1] **The rejected claims include claims 600, 604, 605, 608-611, 614-624, 643, 645, 646, 648-651, 654-670, 709-714, 716, 717, 752, 756, 757, 760-763, 766-776, 786-797, 800-803, 806-822, 868, 869, 903, 904, 908, 909, 912-915, 918-928, 938-947, 949, 950, 952-974, 1013-1018, 1020, 1021, 1056, 1060, 1061, 1064-1067, 1070-1081, 1090-1099, 1101, 1102, 1104-1107, 1110-1126, 1165-1170, 1172, 1173, 1177-1210, 1213-1229, 1232-1246, 1248-1250, 1252, 1253, 1255-1258, 1260-1294, 1296-1329, 1332-1407, 1409, 1410, 1473-1488, 1491-1494, 1497-1568, 1570-1612, 1614-1616, 1619-1634, 1637-1699, 1704-1718, 1723-1728, 1730-1741, 1743 and 1749-1765**

> are incorporated into nucleic acid, but subsequently block further chain growth or interfere with nucleic acid function.[emphasis added]
>
> Most of these compounds were known in the art before the first filing of Applicants' application. A copy of pages 446-449 from Kornberg's DNA Replication is attached as Exhibit 2. Please refer to footnotes 21-29 on pages 447-449.
>
> Since hybridization is a property of the entire polynucleotide chain, the presence of one or more sites within the chain that may be occupied by analogs which are not furanoses, will not necessarily prevent hybridization of the nucleic acid strand to its complement. As alluded to in the Office Action, "spacing linkages" can compensate for the lack of sugar moieties altogether, as in the case of peptide nucleic acids cited by the Examiner.
>
> In light of the foregoing remarks, reconsideration and withdrawal of the enablement rejection is respectfully requested.

Applicants now wish to supplement those remarks above with the remarks that now follow below.

It is textbook knowledge that in addition to their chemical formulae and classification according to carbonyl group and number of carbon atoms, sugars are also conformationally variable, assuming different conformations. These sugar conformations can take various forms which are in equilibrium. See Voet and Voet's Biochemistry [John Wiley & Sons, Inc., New York, 1990, pages 247-252; copy attached as Exhibit A. Thus, the six- and five-carbon sugars, hexoses and pentoses, can assume a six-membered ring (pyranose), and a five-membered ring (furanose). In fact, whether a sugar takes on a pyranose form or a furanose form depends primarily on the particular sugar (monosaccharide) and to a lesser extent on conditions. As described by Voet and Voet (Exhibit A):

> **Sugars are Conformationally Variable**
>
> Hexoses and pentoses may each assume pyranose or furanose forms. The equilibrium composition of a particular monosaccharide depends somewhat on conditions but mostly on the identity of the monosaccharide. For instance, in aqueous solutions, glucose exists almost exclusively in the pyranose form whereas ribose is ~25% furanose and 75% pyranose. . .
>
> [Voet & Voet, Biochemistry, page 249; Exhibit A]

Moreover, the pyranose form is energetically favored over the furanose form as reported by Van Aerschot et al. (1995) ["1,5-Anhydrohexitol Nucleic Acids, a New Promising Antisense Construct," Angew. Chem. Int. Ed. Engl. 34:1338-1339]:

> ***Because pyranose ODNs are energetically favored over furanose ODNs (smaller change in entropy during duplex formation)***, various pyranoses have already been studied.[6] . . . [page 1338; emphasis added]

A copy of Van Aerschot's publication is attached as Exhibit B.

More recently, the need for a sugar moiety in the form of a furanose has been called into question. In a conclusion to his review article ["DNA Analogues: From Supramolecular Principles to Biological Principles," Bioorganic & Medicinal Chemistry 10:841-854 (2002)], Christian J. Leumann discloses:

> Based on these results, we drew the conclusion that ***the structural feature of the furanose unit, as present in the natural nucleosides, is not a necessary prerequisite for obtaining a stable and selective base-pairing system, provided that the C–C bonds participating in the repetitive unit of the phosphodiester backbone are conformationally locked***. Moreover, the information for the preference of antiparallel strand association in DNA must not necessarily be a consequence of the bases being attached to a specific (α or β) side of the furanose unit, but can also be encoded in the backbone itself. Furthermore, conformational flexibility in the base-pairing region does not lead to a loss of selectivity (match vs mismatch) in base-pair formation.
>
> [page 851; emphasis added]

A copy of this year's Leumann's review article is attached as Exhibit C.

Among nucleotide analogs containing six-membered rings which have been found ***not*** to inhibit base-pairing hybridization are the hexitol nucleic acids (HNAs). Van Aerschot et al., discussed *supra*., (Exhibit B) and Hendrix et al. [1',5'-Anhydrohexitol Oligonucleotides: Synthesis, Base Pairing and Recognition by Regular Oligodeoxyribonucleotides and Oligoribonucleotides," Chem. Eur. J. 3:110-

120 (1997)] have both investigated these compounds in terms of base-pairing hybridization.

Van Aerschot (Exhibit A) concludes his article:

> ***These results indicate that ODNs*** [antisense oligodeoxyribonucleotides] ***containing 1,5-anhydrohexitol building blocks form very stable complexes with DNA and RNA*** and are enzymatically stable. Therefore these new constructs fulfill at least two requirements of an ideal antisense construct. [page 1339; emphasis added]

Hendrix et al. concludes his article:

> **Conclusion**
>
> ***Hexitol nucleic acids (HNA) form very stable self-complementary duplexes as well as stable duplexes with their natural counterparts.*** These hybridisation characteristics are dependent and the experimental conditions . . . [page 117, right column; emphasis added]

A copy of Hendrix et al. is attached as Exhibit D.

Finally, before the leaving the matter, other six-membered ring structures have been found useful for base-pairing hybridization. So-called "morpholino subunits" containing a ring nitrogen have been synthesized by converting ribonucleosides. These morpholino derivatives may hybridize even better to complementary target nucleic acids than deoxyribonucleoside-derived oligomers and their targets. In Discoveries In Antisense Nucleic Acids [Christine L. Brakel, Editor, Gulf Publishing Company, Houston, 1989, part of Advances in Applied Biotechnology Series, Volume 2, Chapter 6, "Uncharged Nucleic Acid Analogs for Therapeutic and Diagnostic Applications," pages 71-80], Summerton discloses:

> ***While the ribose-derived morpholino backbone moieties have structures significantly different from the ribose and deoxyribose moieties of natural nucleic acids and most current nucleic acid analogs, molecular modeling of these and a variety of other related morpholino-type oligomers suggested that they should adopt a***

> ***conformation compatible with binding to a complementary nucleic acid target sequence.*** In fact, because the morpholino moiety is likely to adopt preferentially a chair conformation with the purine or pyrimidine base and the 5' methylene (numbered as in the parent ribose) equitorial (in contrast to the multiplicity of nearly equal energy conformations available to ribose and deoxyribose rings), and because the annular nitrogens of the morpholino ring cannot rotate (in contrast to the rotational freedom of the analogous C3'-O3' bond of ribose and deoxyribose), we believe that the ***inherent entropy cost of pairing these morpholino-type Neu-Genes™ to their target genetic sequences is appreciably less than the corresponding entropy cost of pairing deoxyribonucleoside-derived oligomers and their complementary target genetic targets.*** [Summerton, pages 78-79; emphasis added]

A copy of Summerton's chapter is attached as Exhibit E.

In closing, Applicants are offering the above information and exhibits (A-E) to illustrate that other sugar moieties, in addition to the conformational furanose forms, will still permit base-pairing hybridization to proceed between complementary nucleic acid strands and sequences.

III. Previous Submission of Art-Related Documents

In their September 12, 2002 Amendment (pages 24-25), Applicants indicated that several English translations had been ordered and would be submitted to the U.S. Patent Office for consideration by the Examiner. These English translations have now been obtained and are being filed concurrently herewith in Applicants' Seventh Information Disclosure Statement Under 37 C.F.R. §§1.56 & 1.97-1.98. Thus, in their 7th IDS, Applicants are providing foreign documents and English translations for the following:

1. partial English translation of Kagakukai ed., "Fluorescence tagging" Biochemistry Experiments Course 2, Nucleic Acid Chemistry III, pages 299-317 (1977) **[cited but not provided as Exhibit 53 to September 19, 2001 4th**

Supplemental IDS and provided in Applicants' October 9, 2001 Communication To Transmit Documents Cited In Applicants' 4th Supplemental IDS; attached as Exhibit 1 to 7th IDS];

2. Gilbert W., "DNA-sequenzierung und gon-struktur (Nobel-Vortrag)" Angenwandte Chemie 93:1037-1046 (I981) **[cited but not provided as Exhibit 60 to 9/19/01 4th Supplemental IDS and provided in Applicants' October 9, 2001 Communication To Transmit Documents Cited In Applicants' 4th Supplemental IDS; attached as Exhibit 2 to 7th IDS]**;

3. Husimi, Y. "DNA Sequences," Oyo Buturi 51(12):1400 (I982) **[cited but not provided as Exhibit 68 to 9/19/01 4th Supplemental IDS and provided in Applicants' October 9, 2001 Communication To Transmit Documents Cited In Applicants' 4th Supplemental IDS; attached as Exhibit 3 to 7th IDS]**;

4. Ulanov et al., "Electron microscopic determination of guanosine localization in DNA," Biophysics 12:325-326 (1967) **[cited but not provided as Exhibit 72 to 9/19/01 4th Supplemental IDS and provided in Applicants' October 9, 2001 Communication To Transmit Documents Cited In Applicants' 4th Supplemental IDS; attached as Exhibit 4 to 7th IDS]**; and

5. Ulanov et al., "On The Problem Of Determination Of Base Squences In Nucleic Acids," Biophysics 12:326-330 (1967) **[Not cited or provided previously; attached as Exhibit 5 to 7th IDS]**.

Copies of the above-listed 5 documents are being provided as Exhibits 1-5 to Applicants' 7th IDS. A completed Form PTO-1449 is also attached as Exhibit 6.

Favorable action is respectfully sought.

* * * * * * *

SUMMARY AND CONCLUSIONS

New claims 1769-1775 have been added above to the previously pending claims. No claims have been amended or canceled by this paper.

The fee for adding new claims 1769-1775 is $192, based upon the presentation of one additional independent claim [$84 X 1 = $84] and six dependent claims [$18 X 6 = $108]. The Patent and Trademark Office is hereby authorized to charge the requisite $192 claim fee to Deposit Account 05-1135. No other fee or claim fee is believed due in connection with this filing. In the event that any other fee or fees are due, however, The Patent and Trademark Office is hereby authorized to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

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